AHRQ Healthcare Horizon Scanning System – Potential High-Impact Interventions Report

Priority Area 01: Arthritis and Nontraumatic Joint Disease

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Statement of Funding and Purpose

This report incorporates data collected during implementation of the Agency for Healthcare Research and Quality (AHRQ) Healthcare Horizon Scanning System by ECRI Institute under contract to AHRQ, Rockville, MD (Contract No. HHSA290201000006C). The findings and conclusions in this document are those of the authors, who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

This report's content should not be construed as either endorsements or rejections of specific interventions. As topics are entered into the System, individual topic profiles are developed for technologies and programs that appear to be close to diffusion into practice in the United States. Those reports are sent to various experts with clinical, health systems, health administration, and/or research backgrounds for comment and opinions about potential for impact. The comments and opinions received are then considered and synthesized by ECRI Institute to identify interventions that experts deemed, through the comment process, to have potential for high impact. Please see the methods section for more details about this process. This report is produced twice annually and topics included may change depending on expert comments received on interventions issued for comment during the preceding 6 months.

A representative from AHRQ served as a Contracting Officer's Technical Representative and provided input during the implementation of the horizon scanning system. AHRQ did not directly participate in horizon scanning, assessing the leads for topics, or providing opinions regarding potential impact of interventions.

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None of the individuals compiling this information has any affiliations or financial involvement that conflicts with the material presented in this report.

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Preface

The purpose of the AHRQ Healthcare Horizon Scanning System is to conduct horizon scanning of emerging health care technologies and innovations to better inform patient-centered outcomes research investments at AHRQ through the Effective Health Care Program. The Healthcare Horizon Scanning System provides AHRQ a systematic process to identify and monitor emerging technologies and innovations in health care and to create an inventory of interventions that have the highest potential for impact on clinical care, the health care system, patient outcomes, and costs. It will also be a tool for the public to identify and find information on new health care technologies and interventions. Any investigator or funder of research will be able to use the AHRQ Healthcare Horizon Scanning System to select potential topics for research.

The health care technologies and innovations of interest for horizon scanning are those that have yet to diffuse into or become part of established health care practice. These health care interventions are still in the early stages of development or adoption, except in the case of new applications of already-diffused technologies. Consistent with the definitions of health care interventions provided by the Institute of Medicine and the Federal Coordinating Council for Comparative Effectiveness Research, AHRQ is interested in innovations in drugs and biologics, medical devices, screening and diagnostic tests, procedures, services and programs, and care delivery.

Horizon scanning involves two processes. The first is identifying and monitoring new and evolving health care interventions that are purported to or may hold potential to diagnose, treat, or otherwise manage a particular condition or to improve care delivery for a variety of conditions. The second is analyzing the relevant health care context in which these new and evolving interventions exist to understand their potential impact on clinical care, the health care system, patient outcomes, and costs. It is NOT the goal of the AHRQ Healthcare Horizon Scanning System to make predictions on the future use and costs of any health care technology. Rather, the reports will help to inform and guide the planning and prioritization of research resources.

We welcome comments on this Potential High-Impact Interventions report. Send comments by mail to the Task Order Officer named in this report to: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to: effectivehealthcare@ahrq.hhs.gov.

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Background

Horizon scanning is an activity undertaken to identify technological and system innovations that could have important impacts or bring about paradigm shifts. In the health care sector, horizon scanning pertains to identifying new (and new uses of existing) pharmaceuticals, medical devices, diagnostic tests and procedures, therapeutic interventions, rehabilitative interventions, behavioral health interventions, and public health and health promotion activities. In early 2010, the Agency for Healthcare Research and Quality (AHRQ) identified the need to establish a national Healthcare Horizon Scanning System to generate information to inform comparative-effectiveness research investments by AHRQ and other interested entities. AHRQ makes those investments in 14 priority areas. For purposes of horizon scanning, AHRQ's interests are broad and encompass drugs, devices, procedures, treatments, screening and diagnostics, therapeutics, surgery, programs, and care delivery innovations that address unmet needs. Thus, we refer to topics identified and tracked in the AHRQ Healthcare Horizon Scanning System generically as "interventions." The AHRQ Healthcare Horizon Scanning System implementation of a systematic horizon scanning protocol (developed between September 1 and November 30, 2010) began on December 1, 2010. The system is intended to identify interventions that purport to address an unmet need and are up to 4 years out on the horizon and then to follow them up to 2 years after initial entry into the health care system. Since that implementation, review of more than 16,000 leads about potential topics has resulted in identification and tracking of about 1,800 topics across the 14 AHRQ priority areas and 1 cross-cutting area; about 600 topics are being actively tracked in the system.

Methods

As part of the Healthcare Horizon Scanning System activity, a report on interventions deemed as having potential for high impact on some aspect of health care or the health care system (e.g., patient outcomes, utilization, infrastructure, costs) is aggregated twice annually. Topics eligible for inclusion are those interventions expected to be within 0–4 years of potential diffusion (e.g., in phase III trials or for which some preliminary efficacy data in the target population are available) in the United States or that have just begun diffusing and that have completed an expert feedback loop.

The determination of impact is made using a systematic process that involves compiling information on topics and issuing topic drafts to a small group of various experts (selected topic by topic) to gather their opinions and impressions about potential impact. Those impressions are used to determine potential impact. Information is compiled for expert comment on topics at a granular level (i.e., similar drugs in the same class are read separately), and then topics in the same class of a device, drug, or biologic are aggregated for discussion and impact assessment at a class level for this report. The process uses a topic-specific structured form with text boxes for comments and a scoring system (1 minimal to 4 high) for potential impact in seven parameters. Participants are required to respond to all parameters.

The scores and opinions are then synthesized to discern those topics deemed by experts to have potential for high impact in one or more of the parameters. Experts are drawn from an expanding database ECRI Institute maintains of approximately 350 experts nationwide who were invited and agreed to participate. The experts comprise a range of generalists and specialists in the health care sector whose experience reflects clinical practice, clinical research, health care delivery, health business, health technology assessment, or health facility administration perspectives. Each expert uses the structured form to also disclose any potential intellectual or financial conflicts of interest

(COIs). Perspectives of an expert with a COI are balanced by perspectives of experts without COIs. No more than two experts with a possible COI are considered out of a total of the seven or eight experts who are sought to provide comment for each topic. Experts are identified in the system by the perspective they bring (e.g., clinical, research, health systems, health business, health administration, health policy).

The topics included in this report had scores *and/or* supporting rationales at or above the overall average for all topics in this priority area that received comments by experts. Of key importance is that topic scores alone are not the sole criterion for inclusion—experts' rationales are the main drivers for the designation of potentially high impact. We then associated topics that emerged as having potentially high impact with a further subcategorization of "lower," "moderate," or "higher" within the high-impact-potential range. As the Healthcare Horizon Scanning System grows in number of topics on which expert opinions are received, and as the development status of the interventions changes, the list of topics designated as having potentially high impact is expected to change over time. This report is being generated twice a year.

For additional details on methods, please refer to the full AHRQ Healthcare Horizon Scanning System Protocol and Operations Manual published on AHRQ's Effective Health Care Web site.

Results

The table below lists the four topics for which (1) at least preliminary phase III data were available; (2) information was compiled before May 16, 2013, in this priority area; and (3) we received five to nine sets of comments from experts between October 25, 2011, and May 18, 2013. (Eighteen topics in this priority area were being tracked in the system as of May 18, 2013.) Three of the topics emerged as having potential for high impact on the basis of experts' comments and their assessment of potential impact. They are noted by an asterisk in the table below. The material in this Executive Summary and report is organized alphabetically by disease and then intervention. Readers are encouraged to read the detailed information on each intervention that follows the Executive Summary.

Priority Area 01: Arthritis and Nontraumatic Joint Disease

Topic	High-Impact Potential
1. *Artificial cervical disc (Mobi-C) for treatment of two-level degenerative disc disease	Moderately high
2. *Autologous mesenchymal stem cell therapy for osteoarthritis	Moderately high
3. *Autologous platelet-rich plasma therapy for osteoarthritis	Moderately high
4. Tofacitinib (Xeljanz) for treatment of rheumatoid arthritis	No high-impact potential at this time

Discussion

The topics that emerged as higher impact were in disease categories of two-level degenerative disc disease (DDD) and osteoarthritis (OA), conditions in which experts perceived considerable unmet need because of a lack of effective treatments and the impact of OA on quality of life.

Cervical Degenerative Disc Disease

Cervical DDD occurs as part of the normal aging process and affects an estimated two-thirds of people aged 40 years or older in their lifetimes. Cervical DDD occurs when progressive changes in the cervical vertebral discs lead to loss of disc height, loss of water content, loss of shock-absorbing capacity, and bone spur formation. Poor nutrition, smoking, atherosclerosis, physical activity, and

genetics may also contribute the development of DDD. DDD of the cervical spine can result in clinical manifestations including axial neck pain, radiculopathy, myelopathy, or a combination of these conditions. Symptoms can include numbness, pain, or loss of function (e.g., gait issues, grip weakness, bowel and bladder complaints). Cervical DDD is diagnosed with a magnetic resonance imaging (MRI) scan; however, diagnosis must also include history of signs and symptoms and a physical examination. Treatments typically involve pain management, such as oral medication, epidural injections, and trigger-point injections; some patients seek osteopathic manipulation, transcutaneous electrical stimulation, and physical therapy. When these therapies fail to achieve relief, surgical treatments may be proposed, such as arthroplasty and anterior and posterior decompression and fusion. An important and limiting complication of cervical spine fusion surgery is the potential for developing DDD in adjacent discs after surgery. Cervical artificial intervertebral disc arthroplasty is purported to relieve DDD symptoms, preserve range of motion, and prevent development of DDD at adjacent discs. However, according to Walsh as reported at the 2009 California Technology Assessment Forum, some patients with cervical DDD can have signs of degeneration at multiple levels at the time of diagnosis. No options have been approved by the U.S. Food and Drug Administration (FDA) for multilevel cervical disc replacement. One investigational device intended for two-level cervical disc arthroplasty emerging as having potential for high impact.

Artificial Cervical Disc (Mobi-C) for Treatment of Two-Level Degenerative Disc Disease

- **Key Facts**: The Mobi-C artificial cervical disc (LDR Holding Corp., Austin, TX) is an investigational device in trials for cervical disc replacement at two adjacent levels in patients with cervical DDD. The disc is intended to restore segmental motion and disc height and is a semiconstrained prosthesis with a mobile polyethylene insert, capable of sliding, situated between two chrome cobalt plates coated with a titanium plasma spray and hydroxyapatite coating. The design purportedly allows mobility that includes five independent degrees of freedom. The controlled mobility of the insert purportedly helps restore and preserve the instantaneous axis of rotation to restore physiological mobility of the spinal segment. In a randomized controlled trial, patients (n=330) with two-level DDD and radiculopathy or myeloradiculopathy with pain, paresthesias, or paralysis in a specific nerve root distribution (C3–C7) were treated with either cervical disc replacement with Mobi-C or anterior cervical discectomy and fusion (ACDF) with allograft bone and anterior plate. Patients treated with Mobi-C were reported to have a significantly higher success rate than patients treated with ACDF at 6, 12, 18, and 24 months. Additionally, patients treated with Mobi-C were reported to have more improvement than patients treated with ACDF in Neck Disability Index scores at every time point and more improvement in visual analog scale neck pain score at 6 weeks and at 3, 6, and 12 months. Study authors also reported that patients treated with Mobi-C also generally maintained preoperative segmental range of motion at both treated segments immediately after implantation and throughout the 24-month followup. Patients treated with ACDF were reported to need reoperation more often than patients treated with Mobi-C and Mobi-C patients reported fewer complications and adverse events than did ACDF patients. The main mechanical complications reported with Mobi-C were radiological adjacent syndrome and heterotrophic ossification.

  In March 2011, LDR submitted a premarket approval (PMA) application to FDA for Mobi-C for two-level cervical disc replacement. In November 2012, the manufacturer received an approvable letter from FDA. If approved, Mobi-C would be the first cervical

disc to receive FDA approval for two-level use. The manufacturer anticipates approval and U.S. availability of Mobi-C for the two-level disc replacement indication in 2013.

Our searches did not find information on the estimated cost of two-level disc replacement with Mobi-C. Single-level cervical disc replacement was estimated at a Web site accessed in 2013 to cost about $35,000–$45,000 for a single-level procedure. Third-party payers generally deny coverage for two-level disc replacement because they consider multilevel cervical disc replacement to be investigational at this time.

- **Key Expert Comments**: Overall, experts commenting on this intervention stated that a significant proportion of patients with cervical DDD have the disease at two levels and ACDF can result in disc degeneration at adjacent levels. Thus, two-level cervical disc replacement with an effective implant could fulfill a significant unmet need by relieving patients' symptoms, preserving range of motion, and preventing the development of DDD at adjacent discs. Available evidence suggests that Mobi-C appears to provide significant improvements in the clinical success rate and reductions in reoperation rates, complications, and recovery times compared with those outcomes with ACDF at 24-month followup. If the clinical evidence for Mobi-C continues to show favorable outcomes, third-party reimbursement might be more likely, which would remove the barrier of high out-of-pocket patient costs for two-level disc replacement. Based on this input, our overall assessment is that this intervention is in the moderate high-impact-potential range.
- **Potential for High Impact**: Moderately high

Osteoarthritis

OA, the most common form of arthritis, affects an estimated 27 million Americans according to the National Institute of Arthritis and Musculoskeletal and Skin Diseases, and is expected to affect a greater proportion of the population as more people reach age of 65 years or older. OA is a chronic condition characterized by the progressive loss of cartilage in one or more joints. As the cartilage that cushions a joint gradually wears away from use, bones rub against each other, causing pain, stiffness, and loss of joint flexibility. Increasing age, obesity, injury to or overuse of a joint, and genetics can all contribute to the disease. Current treatments for OA include over-the-counter pain medication, exercise and/or physical therapy, and weight loss if indicated. More severe cases may warrant injections with corticosteroids. However these agents have no anabolic or anticatabolic activity on chondrocytes, which are the cells responsible for maintaining cartilage. Two interventions were deemed by experts commenting on them to have potential to disrupt the current OA treatment paradigm because of their purported potential to regenerate articular cartilage or inhibit degenerative processes. These interventions are available both as proprietary autologous products and as autologous biologic products prepared onsite by health care facilities delivering the treatment to patients.

Autologous Mesenchymal Stem Cell Therapy for Osteoarthritis

- **Key Facts**: Autologous mesenchymal stem cell (MSC) therapy for OA consists of adult stem cells derived from the patient's own bone marrow, synovium, periosteum, skeletal muscle, or adipose tissue, and manipulated in any number of ways, including concentrating and culturing the cells to increase their numbers, and combining with growth factors and/or platelet-rich plasma (PRP) and fat matrix. Depending on the amount of processing performed, the preparation is reinjected into the patient's intra-articular space the same day (for preparations that undergo only centrifugation with no additives) or up to a few weeks later (for highly processed, cultured preparations with additives). The methods used to

prepare MSCs have not yet been standardized and differ among facilities making and administering the preparations. This may lead to different outcomes among treatment centers. MSCs are purported to lead to cartilage regeneration because of the secretion of growth factors by the cells or from differentiation of MSCs into chondrocytes. The exact mechanism remains unknown. MSCs are purported to have immunomodulatory, antiapoptotic, proliferative, and angiogenic effects on cells in the intra-articular space. Preliminary evidence suggests that intra-articular injection with some MSC preparations may improve pain, function, and radiologic endpoints, but study results are mixed at this time and controlled trials with standardized MSC preparation methods are needed to determine the their true efficacy. The therapy can conceivably be made and delivered by any suitably equipped health care center, and dozens of orthopedic centers that treat OA have begun to offer it, although FDA requires an investigational new drug application and trials for any autologous cell products that are more than "minimally processed." No company has an FDA-approved autologous MSC product at this point, although one company in Texas has stated intentions to pursue FDA approval. Another company in Colorado that had offered a cultured, highly processed autologous MSC product was ordered by FDA to stop and moved its operations for that product offshore; the company now offers a "minimally" processed product in its centers. Reported costs for the procedure are about $10,000. Our searches of 11 representative, private, third-party payers that publish their coverage policies online showed that all of the payers listing policies for MSCs for OA consider the therapy investigational at this time.

- **Key Expert Comments**: Experts stated that effective, minimally invasive OA therapies that can prevent or delay joint-replacement surgery are needed, especially because many patients with OA are experiencing symptom onset at an earlier age because of active lifestyles. Autologous MSC therapy has potential to be a first-line OA-treatment option if it is shown to reduce pain and regenerate articular cartilage. However, experts were cautiously optimistic about the potential impact of autologous MSC therapy because of the paucity of data demonstrating its ability to relieve symptoms and regenerate cartilage. Diffusion will be tempered by the high out-of-pocket patient costs at this time and until FDA approves a highly processed autologous MSC treatment or evidence demonstrates a clear benefit to patients of clinic-prepared minimally processed autologous MSCs.
- **Potential for High Impact**: Moderately high

Autologous Platelet-Rich Plasma Therapy for Osteoarthritis

- **Key Facts**: Autologous PRP therapy involves processing (centrifuging) the plasma portion of a patient's blood to concentrate and separate out the platelets, which are purported to secrete a wide variety of growth factors and cytokines and are purported by some to promote tissue regeneration and repair. As such, PRP is thought by some researchers to have potential regenerative effects on cartilage in patients with OA. PRP therapy has been used by high-profile athletes in an attempt to speed their recovery process after soft-tissue injuries. PRP, collected from the patient and concentrated, is injected directly into the intra-articular space under ultrasound guidance. As with autologous MSC therapy, preparation protocols and injection frequency vary among treatment centers. The evidence base for PRP lacks sufficiently large, blinded, prospective, randomized controlled trials that compare it to other standard treatments for OA and to autologous MSCs. Our searches of 11 representative, private, third-party payers that publish their coverage policies online found 8 payers that have specific policies denying coverage for the procedure because they consider

PRP injections to be experimental or investigational. The cost of PRP therapy has been reported to range from $500 to $1,500 per injection, and thus, appears to be less costly than autologous MSCs. A patient may choose to receive more than one injection over time.

- **Key Expert Comments**: Overall, experts were divided on the impact that PRP might have on OA treatment. Similar to the experts' comments on autologous MSC therapy, several experts stated that if PRP were to be proved effective and became accepted first-line therapy that could regenerate joint cartilage and restore function, its impact would be major on patient outcomes and costs of treating OA. However, more data and clinical experience are needed to standardize preparation procedures and regimens and test those regimens in randomized controlled trials to determine whether the procedure regenerates cartilage, has a more durable effect and reduces the need for additional OA treatment for the affected joint, compared with other standard therapies for OA.
- **Potential for High Impact**: Moderately high

Cervical Degenerative Disc Disease Intervention

Artificial Cervical Disc (Mobi-C) for Treatment of Two-Level Degenerative Disc Disease

Unmet need: Cervical degenerative disc disease (DDD) occurs naturally as part of the aging process and may affect up to two-thirds of people aged 40 years or older in their lifetimes.[1] DDD of the cervical spine can result in clinical manifestations including axial neck pain, radiculopathy, myelopathy, or a combination of these conditions.[1] Anterior cervical discectomy and fusion (ACDF) is the gold standard for treating cervical DDD at single or multiple levels.[2] But cervical spine fusion surgery has is an important and limiting complication, the potential for developing DDD in adjacent discs after surgery, and some patients with cervical DDD can have signs of degeneration at multiple levels at the time of diagnosis.[2] Cervical artificial intervertebral disc arthroplasty is purported to relieve DDD symptoms, preserve range of motion, and prevent the development of DDD at adjacent discs. No approved options exist for multilevel cervical disc replacement.[3]

Intervention: The Mobi-C artificial cervical disc is an investigational device intended for cervical disc replacement at two adjacent levels in patients with cervical DDD.[3] The device was purportedly designed for cervical intervertebral disc replacement to restore segmental motion and disc height.[4] The device is a semiconstrained prosthesis with a mobile polyethylene insert, capable of sliding, situated between two chrome cobalt plates coated with a titanium plasma spray and hydroxyapatite coating.[4,5] Mobi-C is intended for use in both one- and two-level cervical intervertebral disc replacement.[4]

The design purportedly allows mobility that includes five independent degrees of freedom—two translational and three rotational.[5] The controlled mobility of the insert purportedly helps restore and preserve the instantaneous axis of rotation and physiologic mobility of the spinal segment.[4] Whereas cervical discs commonly use keels or screws for fixation, Mobi-C was designed with the intention of accomplishing the following:

- Minimize stresses between the implant and bone via the mobile core, to eliminate the need for more-invasive fixation mechanisms[6]
- Eliminate the need for invasive vertebral anchorage
- Preserve vertebral endplate integrity[3]

The device's lateral teeth have an inclined shape that purportedly facilitates the insertion of the device and provides secure anchoring to the peripheral vertebral plate.[3]

The device is delivered in sterile packaging and assembled and maintained between two Plug & Fit®, one-time use, radiotransparent clamps, which are used for proper device placement.[3] The patient is placed in the supine position and an image intensifier is placed under the operative drapes for the duration of surgery. The surgeon makes an incision in a skin fold of the neck over the anterior edge of the sternocleidomastoid muscle if only one level is required. A vertical incision is used if two or more disc replacements are required. When the anterior column is attained, the longus colli muscles are carefully dissected.[3] Radiotransparent retractors are placed under the two longus colli muscles and an anterior discectomy and replacement is performed.[3]

Clinical trials: In a randomized controlled trial, patients (n=330) with two-level DDD and radiculopathy or myeloradiculopathy with pain, paresthesias, or paralysis in a specific nerve root distribution (C3–C7) were treated with either Mobi-C (n=225) or ACDF (n=105) with allograft bone and anterior plate. The success rate for patients treated with Mobi-C was reported as 70.59% compared with 36.36% for ACDF at 24-month followup ($p<0.001$).[7] Statistical superiority was also demonstrated at earlier time points. The difference between Mobi-C and ACDF success rates at 6,

12, and 18 months were +49.4%, +37.8%, and +29.9%, respectively ($p<0.001$ for all comparisons).[7] The authors reported that, "On average, patients in both groups showed significant improvements in NDI [neck disability index] score, VAS [visual analog scale] neck pain, and VAS arm pain from pre-operative baseline at all time points. However, the TDR [total disc replacement] patients experienced significantly more improvement than ACDF patients in NDI score at all time points and significantly more improvement in VAS neck pain score at 6 weeks, and 3, 6, and 12 months. Patients in the TDR group also on average maintained pre-operative segmental range of motion at both treated segments immediately postoperatively and throughout the study period of 24 months." Patients treated with ACDF required reoperation more frequently (11.4%) than patients treated with Mobi-C (3.1%; $p<0.05$).[8,9]

Patients treated with Mobi-C reported fewer complications than patients treated with ACDF.[8] At 24 months, 5.3% of the Mobi-C group and 5.7% of the ACDF showed deterioration in neurological assessments from preoperative baseline. Through 24 months, 21.4% of the Mobi-C group and 30.5% of the ACDF group reported at least one serious adverse event. In the Mobi-C group, 10 serious adverse events in 7 patients were assessed as probably or definitely related to the device; in the ACDF group, 23 serious adverse events were noted in 13 patients, a statistically significant difference between groups on both subject and event levels.[8]

The main mechanical complications associated with disc replacement with Mobi-C included radiological adjacent syndrome and heterotrophic ossification; class III events were reported as permitting residual movement.[5,10]

Manufacturer and regulatory status: LDR Holding Corp., of Austin, TX, is developing the Mobi-C cervical artificial disc. In March 2011, LDR submitted a premarket approval (PMA) application to the U.S. Food and Drug Administration (FDA) for Mobi-C for two-level cervical disc replacement.[11] In November 2012, the manufacturer received a letter from FDA stating that the application was "approvable" for use in two-level cervical disc replacement. This means that FDA can schedule it for consideration for approval. If approved, Mobi-C would be the first artificial cervical disc to receive FDA approval for two-level use.[12] If approved, the manufacturer anticipates that the Mobi-C for two-level disc replacement would be available before the end of 2013.[12]

Diffusion: Our searches did not find information on the estimated cost of two-level disc replacement with Mobi-C. For benchmarking purposes, ACDF for single- or two-level fusion was estimated in a 2009 publication to cost between $10,000 and $15,000.[13] Cervical disc replacement surgery was estimated at a Web site accessed in 2013 to cost about $35,000–$45,000 for a single-level procedure.[14] Although the upfront costs of cervical disc replacement may be higher than for ACDF, these initial costs could be offset by reductions in the numbers of patients requiring revision surgery after ACDF or in reduced rates of damage to adjacent discs.

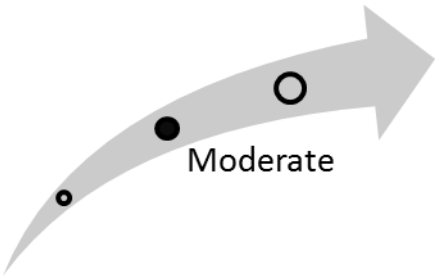
Our searches of 11 representative, private, third-party payers that publish their coverage policies online (i.e., Aetna, Anthem, Blue Cross/Blue Shield Alabama, Blue Cross/Blue Shield Massachusetts, CIGNA, HealthPartners, Humana, Medica, Regence, United Healthcare, Wellmark) found all 11 have specific policies that deny coverage because they consider multilevel cervical disc replacement investigational.[15-25]

Clinical Pathway at Point of This Intervention

Common cervical DDD treatments include medications, osteopathic manipulations, epidural injections, trigger-point injections, transcutaneous electrical stimulation, and physical therapy. Because smoking has been shown to inhibit spinal healing, physicians also encourage smokers in this population to quit.[26] Surgical treatments are rare, but may be required to help control symptoms

and allow a patient to function fully;[26] they include arthroplasty, anterior and posterior decompression, and fusion surgery.[1]

Figure 1. Overall high impact potential: Artificial Cervical Disc (Mobi-C) for treatment of two-level degenerative disc disease



Overall, experts commenting on this intervention stated a significant proportion of patients have two-level DDD and that ACDF can result in disc degeneration at adjacent levels. Thus, two-level Mobi-C Cervical Disc replacement could fulfill a significant unmet need by relieving symptoms, preserving range of motion, and preventing deterioration at adjacent discs. Available evidence suggests that Mobi-C may improve clinical success rates and reduce reoperation rates, complications, and recovery times compared with those outcomes with ACDF. If the clinical evidence for Mobi-C continues to show favorable outcomes, third-party payment, which is lacking now, might follow. Lack of payer coverage appears to be the largest barrier to acceptance and diffusion because of high out-of-pocket costs that patients would otherwise incur. If Mobi-C is shown to improve outcomes enough to benefit patients and reduce the need to reoperate for adjacent DDD after fusion, two-level disc replacement could gain wider acceptance. Based on this input, our overall assessment is that this intervention is in the moderate high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, offered comments on this intervention.[27-32] We organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: Multilevel DDD presents a significant unmet need for new treatment options because ACDF can lead to degeneration at discs above and below the operation site, the experts stated. Complications from ACDF often require additional surgery, one clinical expert noted. Two-level cervical disc replacement with Mobi-C appears to provide a lower rate of complications and reoperations compared with ACDF treatment, experts noted. Two-level disc replacement was also reported as providing improved range of motion, which might reduce complications and future operations, one clinician stated. However, the experts stated more studies comparing Mobi-C to ACDF are needed to confirm these preliminary results.

Acceptance and adoption: Clinicians are generally expected to accept the procedure if the evidence continues to demonstrate superior efficacy and mobility with fewer complications than ACDF, the experts thought. However, some clinicians may be reluctant to put time into learning a new technique if they think ACDF provides successful treatment most of the time, one research expert stated. Patients are expected to be hesitant about any cervical spine surgery, because of the risk of complications to spinal nerves, one clinical expert stated. Lack of reimbursement and the classification of multilevel disc replacement as investigational by third-party payers may present a significant barrier to acceptance and diffusion for both patients and clinicians. Additional clinical

evidence of improved outcomes and reduced costs of care could increase acceptance by payers and, ultimately, patients and clinicians.

According to some experts, increased training and time required for more complicated surgical procedures are expected to increase the cost of care. However, these costs could be offset by improved surgical outcomes, reduced complications and length of stay, shorter duration of physical therapy, and reduced need for revision surgery. Those factors might increase payer acceptance, thought one clinical expert.

Health care delivery infrastructure and patient management: Offering Mobi-C at surgical centers would require additional training for physicians and staff, the experts stated. Additionally, surgical procedures are expected require more time, increasing demands on surgical suites that offer the procedure. However, these demands could be offset by improved surgical outcomes, reduced patient stays and complications, and a lower rate of additional surgeries required, the experts stated.

Health disparities: Mobi-C could increase health disparities, according to expert comments. The experts thought that the complexity of the procedure would limit diffusion to specialty centers and further, that the current lack of reimbursement for two-level cervical disc replacement surgery and the total out-of-pocket cost of surgery indicate that only wealthy patients would be expected to receive treatment with this procedure until widespread acceptance and coverage from public and private payers occurs.

Osteoarthritis Interventions

Autologous Mesenchymal Stem Cell Therapy for Osteoarthritis

Intervention: Mesenchymal stem cells (MSCs) are adult stem cells that are involved in maintaining the relative stability of internal physiologic conditions of many tissue types in the body.[33] As progenitor cells, MSCs are purported to retain the ability to differentiate into a number of cell types, including chondrocytes, which are the cells responsible for maintaining cartilage.[34,35] Autologous MSCs are derived from the patient and can be isolated, concentrated, cultured, and expanded in vitro and returned to the patient with the intention of treating large cartilage defects observed in osteoarthritis (OA). However, the mechanism by which these cells lead to cartilage generation is still unclear.[33] MSCs may differentiate into chondrocytes and fill in a cartilage defect. Additionally, MSCs are known to have effects on the intra-articular environment, including immunomodulation, host cell survival, proliferation of endogenous tissue progenitor cells, local angiogenesis, and inhibition of fibrosis.[33]

The methods used to prepare autologous MSCs have not yet been standardized; the cells can be isolated from bone marrow, synovium, periosteum, skeletal muscle, or adipose tissue.[34] MSCs isolated from these different tissues purportedly exhibit differences in their ability to proliferate and/or their propensity to differentiate into chondrocytes.[34] To have an adequate number of MSCs for treatment, the cells from a tissue sample must be concentrated by centrifugation and/or expanded in vitro through the culture and addition of growth factors, sometimes including platelets.[35,36] The method chosen to acquire cells may also influence the nature of the MSCs used for treatment. Additionally, patient characteristics such as age and the presence of OA have been shown to affect the ability of autologous MSCs to differentiate into chondrocytes.[34,37] Thus, many factors can introduce variability in this procedure. Autologous MSCs have also been given with other therapies, including platelet-rich plasma (PRP) therapy.

Clinical trials: Many case series have been published, but no definitive, well-designed, controlled trials using standardized methods of preparation are available yet. In one trial, patients (n=18) who received intra-articular injections of adipose-derived autologous MSC combined with PRP, after arthroscopic débridement, for treating knee OA experienced the following:[38]

- A significant decrease in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores from 49.9 points at baseline to 30.3 points at the mean followup of 24.3 months ($p<0.001$)
- Improvement in Lysholm scores from a mean baseline value of 40.1 points to 73.4 points at the last followup ($p<0.001$)
- Improvements in mean VAS score from 4.8 at baseline to 2.0 at the last followup ($p=0.005$)
- Improvement in the whole-organ magnetic resonance imaging (MRI) score from 60.0 points at baseline to 48.3 points at the last followup ($p<0.001$) (clinical significance uncertain)
- Improvement in the cartilage whole-organ MRI score from 28.3 points at baseline to 21.7 points at the last followup ($p<0.001$) (clinical significance uncertain)

Improvements in clinical and MRI results were purported to be positively related to the number of stem cells injected.[38]

In patients with knee OA and a Kellgren-Lawrence status of 2, 3, or 4 (n=23) who were treated with a combination of autologous MSC (concentrated bone marrow isolate), PRP, and fat matrix injected into the intra-articular space, improvements in several disease measures were reported for patients at 6-month (n=12) and 12-month (n=10) followup. The investigators reported that patients treated with MSC therapy had the following:[36]

- Improvements from baseline in patient pain, measured on a VAS, of 34% and 25% at 6 and 12 months, respectively
- Improvements in patient global assessment of disease of 33% and 33% from baseline at 6 and 12 months, respectively
- Improvements in physician global assessment of 51% and 53% from baseline at 6 and 12 months, respectively
- Improvements in 50-foot walk pain of 26% and 17% from baseline at 6 and 12 months, respectively
- Improvements in WOMAC scores of 20% and 8% from baseline at 6 and 12 months, respectively

Additionally, ultrasound measurement of patellofemoral cartilage thickness at seven standardized points revealed that patients treated with MSC had a 0.4 mm and 0.8 mm mean improvement from baseline to 6 months and 12 months, respectively.[36]

Manufacturer and regulatory status: FDA categorizes therapeutic stem cell–based products as human cells, tissues, and cellular and tissue-based products (HCT/Ps), which it defines as "articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient."[39]

Whether an HCT/P is subject to FDA regulation as a biological product, drug, or device depends on how much it has been manipulated after collection. These products are regulated under the authority of both the Public Health Service Act and the Federal Food, Drug, and Cosmetic Act (FDCA).[40] FDA contends that most of the autologous MSCs used for OA "are highly processed, are used for other than their normal function, are combined with non-tissue components, or are used for metabolic purposes" and are subject to regulation.[39,40] Thus, they are subject to requirements for filing as an investigational new drug (IND), investigational device exemption (IDE), or new biologic, depending on how FDA categorizes the product and which division has product oversight. Considerations addressed in FDA's decision to regulate HCT/Ps include the following:[41]

- Has the product been more-than-minimally manipulated (i.e., processing has altered the biological characteristics)?
- Is the product intended for homologous function?
- Has the product been combined with any nontissue or noncellular components?
- Does the product's overall effect on the physiology depend on the body's metabolism?

In 2010, FDA filed an injunction against manufacturer Regenerative Sciences, Inc., of Broomfield, CO, asserting that its stem cell products were considered drugs according to the FDCA and biological products under the Public Health Service Act and that the company was manufacturing these agents without FDA approval, without following good manufacturing practice, and without proving the treatment's safety and efficacy.[42] The company contended that its autologous MSC therapy represented a "practice of medicine" under Colorado state law, and so was not subject to FDA oversight.[43,44] On July 23, 2012, the U.S. District Court for the District of Columbia ruled that the company's ex vivo expansion and manipulation of autologous MSCs exceeded minimal processing and, thus, was subject to FDA regulatory oversight.[45] The court also stated that the presence of the antibiotic doxycycline (which had been shipped in interstate commerce and was added to the cell culture) made the cell product subject to regulation under the FDCA and the Public Health Service Act.[43] The court granted FDA a permanent injunction against Regenerative Sciences for use of Regenexx™ MSCs unless the company completes the required FDA regulatory approval processes.[43]

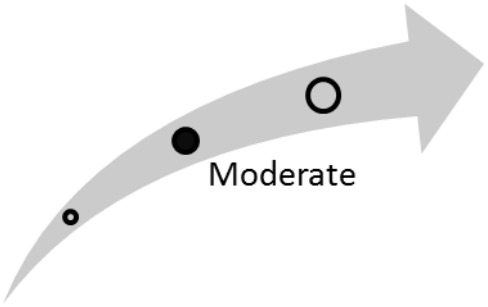
The company continues to offer a modified Regenexx procedure, which it states consists of MSCs derived from bone marrow aspirate and venous blood that are collected processed and injected the same day.[46] The manufacturer states that the new Regenexx procedure offered in the United States is compliant with Code of Federal Regulations 21 Part 1271, which sets forth HCT/P regulations,[47] falling under part 1271.15 (b), which exempts establishments that remove HCT/Ps from an individual and implant them into the same individual during the same surgical procedure.[48,49] At least 14 medical facilities on the East Coast offer the Regenexx procedure.[50]

Diffusion: Although the efficacy of autologous MSCs treating OA has not yet been established, the treatment could conceivably be performed at any suitably equipped health care center, and some physicians have begun to offer it as a treatment.[51,52] One center offering MSC therapy quoted a price of about $10,000 for a regimen that involves a single injection of a bone marrow concentrate, PRP, and autologous fat scaffold plus the required pretreatment and posttreatment assessments.[53,54] Our searches of 11 representative, private, third-party payers that publish their coverage policies online (i.e., Aetna, Anthem, Blue Cross/Blue Shield Alabama, Blue Cross/Blue Shield Massachusetts, CIGNA, HealthPartners, Humana, Medica, Regence, United Healthcare, Wellmark) found that 5 deny coverage for MSC therapy for OA, stating that MSC therapy is investigational because of insufficient evidence or insufficient long-term safety or efficacy outcomes.[55-59]

Clinical Pathway at Point of This Intervention

Patients with OA are often prescribed nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin, ibuprofen, nabumetone, and naproxen as well as the COX-2 inhibitor celecoxib. Physicians can recommend exercise, physical and/or occupational therapy, and weight loss. More severe cases of OA may warrant using prescription painkillers, corticosteroid injections, or viscosupplementation. For patients with severe, persistent symptoms despite optimal treatment, clinicians can recommend surgery, including joint replacement.[60] MSC therapy is intended to be used as a cartilage-restoring technique in patients with uncontrolled OA pain whose disease is not responding to conservative therapy and who do not want to undergo knee replacement.

Figure 2. Overall high-impact potential: autologous mesenchymal stem cell therapy for osteoarthritis



Experts commenting on this technique stated that effective, minimally invasive OA therapies that can prevent or delay joint-replacement surgery are needed, especially because OA is expected to continue to increase in prevalence, including in younger patients. Autologous MSCs have the potential to be the first treatment for OA that could regenerate articular cartilage. However, data are limited regarding the ability of autologous MSCs to improve OA symptoms and regenerate cartilage, and experts were cautious in their assessment of MSC therapy's potential impact. Additionally, the current lack of third-party payer coverage and high out-of-pocket costs for patients are expected to temper the impact of autologous MSC therapy for OA until more evidence

accumulates to demonstrate whether it has clinical benefit. Based on this input, our overall assessment is that this intervention is in the moderate high-impact-potential range.

Results and Discussion of Comments

Seven experts, with clinical, research, health systems, and health administration backgrounds, offered perspectives on this intervention.[61-67] We organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: Current OA therapies treat only the symptoms and do not restore cartilage or joint function, the experts stated; thus, a significant unmet need exists for treatments that can restore cartilage and obviate or delay the need for joint replacement. Additionally, two experts representing a health systems perspective noted the median age for OA onset has declined, the number of patients with OA has increased, and the number of patients with OA is expected to continue to increase in the coming decade, adding to the urgency of addressing this unmet need. Overall, experts stated that effective OA therapies that can prevent joint-replacement surgery are needed.

In terms of health outcomes, preliminary data were encouraging, the experts said, and they were cautiously optimistic about the potential of MSCs to improve patient health outcomes. They thought MSCs could potentially relieve symptoms and regenerate cartilage, providing a novel treatment option to reverse the disease course of OA and reduce the need for additional therapies. But two experts representing a health systems perspective noted that the most positive data were from trials of MSCs combined with PRP and fat matrix, complicating analysis of the effect of MSC therapy alone.

Acceptance and adoption: The experts opined that clinicians would accept MSC therapy if the procedure were to be found safe and effective in larger, randomized clinical trials, because MSC therapy is less invasive than joint-replacement surgery. However, an expert representing a health systems perspective stated that regulatory issues and the poorly defined impact of harvesting MSC from different anatomical sites on cellular differentiation and function in the body could reduce clinician acceptance.

Experts did not see a clear path to patient acceptance of MSC therapy. Patients with OA pain that does to respond to conventional therapy are likely to accept whatever treatment is recommended by their clinicians, the experts thought. However, they noted the need for bone marrow harvest could be a significant barrier to patient acceptance. Additional barriers are the current lack of reimbursement and high out-of-pocket cost of the procedure, limited availability of the procedure, and the experimental nature of stem cells. Still, some patients may be highly interested in new, effective, nonsurgical treatment for their OA, the experts indicated. Clinicians were expected to be more likely to suggest PRP in younger patients with OA who may have an active lifestyle and want to delay joint-replacement surgery.

MSC could be the first treatment option for OA that could regenerate cartilage; however, data are limited. Thus, experts were cautiously optimistic about the potential impact of MSC therapy while the evidence base increases.

Health care delivery infrastructure and patient management: Changes in infrastructure, such as buying equipment and creating facilities to handle and isolate MSCs in an FDA-compliant manner, will be needed in many locations where there may already be demand for the procedure, even though MSC injection is similar to other injections used to treat OA, the experts stated. Allogeneic MSCs are expected by some experts to require less infrastructure expansion by treatment facilities than autologous MSCs.

The experts stated that MSC therapy could reduce the cost of care if the procedure can reduce or delay the need for joint-replacement surgery. If favorable cost-effectiveness data become available for MSC therapy, payers may cover the procedure, which could lower costs for patients. One expert representing a research perspective stated that if MSC therapy can be used in earlier stages of the disease and in younger patients and if MSC can prevent disease progression, it could increase patients' ability to exercise and improve their mental well-being, which could reduce health care costs.

In terms of patient management, experts were divided on the role MSC therapy may play in treating OA. Four experts, representing clinical, research, health systems, and health administration perspectives, stated that if it becomes the first therapy shown to regenerate joint cartilage and restore function, MSC therapy could provide a major advance in treatment for many patients, allowing them to avoid the cost and complications of joint-replacement surgery. Similarly, another expert, representing a research perspective, stated that MSC could bridge the gap between pain-relief treatments and joint-replacement surgery. In contrast, a clinical expert stated that MSC therapy would be used only as an adjunct treatment for patients whose disease is refractory to microfracture surgery. Along the same lines, an expert representing a health systems perspective stated that several treatments for OA are available and this would be viewed as an additional option.

Health disparities: If the procedure is adjunctive to current therapies it could increase health disparities by adding to costs. Some experts agreed that lack of third-party payment for MSC therapy and its implementation in specialty centers are more likely to create health disparities in treating OA.

Autologous Platelet-Rich Plasma Therapy for Osteoarthritis

Intervention: PRP involves processing a plasma portion of a patient's blood to achieve a higher-than-normal concentration of platelets, which are purported to secrete a wide variety of growth factors and cytokines and may promote tissue regeneration and repair.[68] As such, PRP is thought by some investigators and clinicians to have potential to address the underlying pathology of OA rather than only ameliorating symptoms of the disease.[69] PRP has been used in a number of hemostatic applications as well as for treating soft-tissue injuries such as tendinitis and chronic wounds.[68]

In PRP, patient blood is collected and centrifuged to concentrate platelets in a small volume of plasma (about 5 mL) for each injection; clinicians inject it into the patient's intra-articular space under ultrasound guidance.[69-72] Typically, multiple injections are given over the course of several weeks.

Clinical trials: In one trial, patients (n=120) with knee OA Kellgren and Lawrence grade 1, 2, or 3 were treated with three intra-articular injections of PRP or hyaluronic acid. Statistically significant improvements in the WOMAC and Numeric Rating Scale scores were observed in patients who received PRP injections at 3- and 6-month followup. No severe adverse events were observed by the investigators.[73]

In a randomized, double-blind, controlled trial, patients (n=109) with knee OA Kellgren-Lawrence grade 1, 2, or 3 were treated with three weekly injections of PRP or hyaluronic acid and evaluated at 12-month followup. Both groups showed clinical improvement at followup with no statistical difference between groups. The authors reported a "trend" for improvement in the PRP group patients with low-grade articular degeneration (Kellgren-Lawrence score up to 2). No serious adverse events were reported. Mild pain and effusion after the injections were reported, more in the PRP group than in the hyaluronic acid group (p=0.039).[74]

In a retrospective analysis, study authors compared consecutive patients with primary knee OA (n=86) treated by intra-articular PRP injection with similar patients concurrently treated with hyaluronic acid injection (n=21) three times, with 1 week between injections. Authors reported the mean VAS scores to measure pain severity (lower scores show improvement)[75] were as follows:[76]

- At baseline, 8.2 (range 7–10)
- At 12 weeks after treatment, 3.2 (range 1–4)
- At 24 weeks after treatment, 2.9 (range 0–4)

They also reported the mean International Knee Documentation Committee (IKDC) knee scores (higher scores denote greater function) were as follows:[76]

- At baseline, 57.5 points (range 32–77)
- At 12 weeks after treatment, 77.3 points (range 60–95)
- At 24 weeks after treatment, 88.9 points (range 69–98)

Patients receiving PRP were reported to have significant improvements in VAS and IKDC score measures compared with those outcomes in patients receiving hyaluronic acid injection. Both groups had similar safety profiles.[76]

In a study of patients with knee OA (n=261 patients with Outerbridge grades I–IV and symptoms of more than 3 months' duration) who were treated with three intra-articular PRP injections every 2 weeks, 6-month followup showed statistically significant improvements in the PRP group for pain, stiffness, and functional capacity ($p<0.0001$).[77] No adverse events were reported.

In another trial, patients with knee OA (n=100 patients, 115 knees) received three intra-articular PRP injections. Statistically significant improvements in all clinical scores (IKDC form, EQ VAS

quality of life score) were reported between the baseline evaluation, the end of the therapy, and between baseline and 6- and 12-month followup ($p<0.0005$).

In the trial, the results declined significantly by and after 12-month followup ($p=0.02$) but were still better than at baseline ($p<0.0005$).[70] By 24-month followup, all evaluated outcomes were significantly lower than those observed at 12-month followup. Better results were obtained in younger patients ($p=0.0001$) and in patients with lower degrees of cartilage degeneration ($p<0.0005$). The median duration of the clinical improvement provided by PRP for knee OA was 9 months.[72]

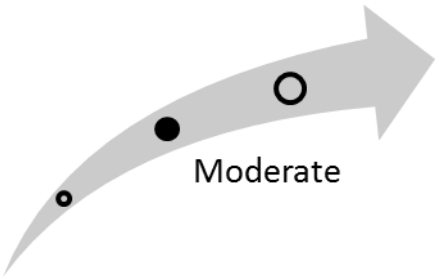
Manufacturer and regulatory status: Autologous PRP is not considered a drug or a therapeutic substance by FDA; therefore, the preparation is not subject to regulatory marketing approval. The patient undergoes apheresis to collect blood to yield the plasma that is centrifuged to concentrate platelets at a facility (such as a hospital blood bank or blood processing laboratory) according to standard blood-processing safety procedures. Thus, the treatment is readily available and may be employed by physicians.[68] Many devices have FDA marketing approval for use in preparing PRP.[70]

Diffusion: The therapy's cost reportedly is from $500 to $1,500 per injection.[78] Our searches of 11 representative, private, third-party payers that publish their coverage policies online found 8 payers that have specific policies denying coverage for the procedure because they consider PRP injections to be experimental or investigational.[79-86]

Clinical Pathway at Point of This Intervention

Patients with OA are frequently prescribed NSAIDs such as aspirin, ibuprofen, nabumetone, and naproxen as well as the COX-2 inhibitor celecoxib. Physicians can recommend exercise, physical and/or occupational therapy, and weight loss. More severe cases of OA may warrant using prescription painkillers, corticosteroid injections, or viscosupplementation. For patients with severe, persistent symptoms despite optimal treatment, clinicians can recommend surgery, including joint replacement.[60] If proved effective for treating knee OA, PRP therapy would be employed as a cartilage-restoring technique in patients with uncontrolled OA pain whose disease is not responding to conservative therapy.

Figure 3. Overall high-impact potential: autologous platelet-rich plasma therapy for osteoarthritis



Overall, experts commenting on this intervention were divided on the impact that PRP might have on OA treatment. Treatment options that can restore cartilage and bridge the gap between pain relief and joint replacement are needed, and several experts stated that if PRP were to become standard first-line therapy and actually regenerate joint cartilage and restore function, it would have a large impact on patient outcomes and be a major cost-saving advance in OA treatment. However, more data and clinical experience are needed to demonstrate whether the procedure regenerates cartilage, has a durable effect, and reduces the need for additional OA treatment for the affected

joint. Based on this input, our overall assessment is that this intervention is in the moderate high-impact-potential range.

Results and Discussion of Comments

Seven experts, with clinical, research, health systems, and health administration backgrounds, offered perspectives on this intervention.[87-93] We organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: Current therapies for OA treat only the symptoms and do not restore cartilage or joint function, the experts stated. Thus, a significant and growing unmet need exists for noninvasive treatments that can restore joint cartilage and function and delay or eliminate the need for joint replacement surgery.

Experts were cautiously optimistic about PRP therapy's potential to improve patient health outcomes by relieving symptoms, regenerating cartilage, and preventing or delaying joint-replacement surgery. However, some experts stated that large, randomized, double-blind controlled trials are needed to better understand PRP's effects on knee and hip OA. One health systems expert stated that data from current trials suggest that the effects of PRP might last for only 6–9 months, which suggests PRP has only moderate potential to improve health outcomes.

Acceptance and adoption: PRP may provide the most clinical benefit in younger patients, which could affect the impact and diffusion of the intervention, the experts theorized. Cost could also affect acceptance. Experts stated that the PRP-injection technique could gain broader acceptance if it is shown to be effective in well-designed controlled trials and if that results in third-party payer coverage. One clinical expert also thought that PRP costs were high for a treatment that had only subjectively reported results. However, if the procedure can eliminate the need for joint-replacement surgery in some patients, PRP injections are expected to be cost saving.

Health care delivery infrastructure and patient management: Because patients with OA already have the option of treatment delivered by injections in the knee or hip, minimal changes in infrastructure and patient management would be seen with implementing PRP, experts thought. However, changes in patient management and infrastructure might occur because of fewer joint-replacement surgeries, which would cause many inpatient procedures to be handled as outpatient procedures, reducing costs. Additionally, some equipment may need to be purchased for preparing PRP, and staff would need training to handle blood collection and prepare PRP.

Health disparities: The effect of this intervention on health disparities is unclear. Two experts with research and systems perspectives stated that the simple, minimally invasive nature of the procedure might enable easy adoption of the procedure in underserved areas. Other experts thought the lack of reimbursement currently associated with the procedure would increase health disparities if the procedure improves outcomes.

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